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(57) Abstract

Aqueous, non-toxic, hypotonic compositions of a quaternary ammonium antimicrobial agent for ophthalmic use are disclosed. These compositions contain an effective amount of non-ionic surfactant to enhance the antimicrobial activity of the quaternary ammonium agent and possess excellent disinfection efficacy for contact lenses.

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CONTACT LENS DISINFECTING COMPOSITIONS

Background

This invention relates to an ophthalmic composition and method for disinfecting contact lenses. More particularly, this invention relates to an ophthalmic composition and method for disinfecting contact lenses which employs an antibacterial and antifungal quaternary ammonium agent in combination with a non-ionic surfactant which achieves a potentiation of the antibacterial and antifungal activities of the quaternary ammonium agent.

Related Art

Historically, contact lenses have fallen into two categories, hard contact lenses and soft contact lenses. The hard contact lenses originally in use were formed from the polymerization of methylmethacrylate to polymethylmethacrylate (PMMA). The soft contact lenses are made of polymerized hydrophilic or hydrophobic monomers. Hydrophilic soft contact lenses are usually based on polyhydroxylated alkyl methacrylates such as 2-hydroxyethyl-methacrylate (HEMA). Presently, rigid and semirigid gas permeable contact lenses made from silicone acrylate and fluoropolymers and the like have largely replaced PMMA contact lenses.

Hard and rigid or semirigid gas permeable contact lenses do not absorb appreciable amounts of water and thus the selection of suitable disinfecting agents, cleaning agents or other lens care solutions is not as critical as it is for soft contact lenses.

Unlike other lenses, soft contact (hydrophilic) lenses absorb water and may take up chemicals used to disinfect and preserve the lens. These chemicals tend to adsorb on lens surfaces and absorb inside the lens

matrix. Such sorption may cause corneal inflammation and other eye tissue irritation.

Despite the softness and optical suitability, one drawback associated with the use of soft contact lenses is the limited availability of safe, simple and reliable methods for their disinfection and cleaning.

Effective disinfection of contact lenses requires both antibacterial and antifungal activity in order to provide maximum safety from ocular infection and lens spoilage.

Soft lenses may be disinfected by thermal treatment with a sterile saline solution. This method is effective in killing pathogens, but may cause distortion and discoloration of the lens.

Hydrogen peroxide, because of its good antimicrobial activity against both bacteria and fungi, has been used to disinfect soft contact lenses. However hydrogen peroxide accumulates in soft contact lenses and moreover has a pH of about 3 which is too acid for ocular tolerance. Hydrogen peroxide is also chemically toxic. It is therefore necessary to neutralize the hydrogen peroxide associated with the lenses with a catalase solution or other suitable neutralizing agent before the lenses can be worn. This two-step procedure is not only laborious, but also potentially dangerous for the wearer who does not properly neutralize the lenses.

The most commonly used soft contact lense chemical disinfectants in the past were thimerosal (sodium ethylmercurithiosalicylate), tris (2-hydroxyethyl) tallow ammonium chloride (disclosed in U.S. Patent No. 4,029,817 to Blanco and known commercially as Miramine) and chlorhexidine. These compounds were originally used in combination, with thimerosal being combined with tris (2-hydroxethyl)-tallow ammonium chloride and chlorhexidine, respectively. This was done because the latter

two disinfectants were not known to have significant antifungal activity; whereas, thimerosal has significant antifungal activity. These early disinfecting solutions suffered from drawbacks of high ocular toxicity due to the relatively high concentrations of the non-mercurial agents used as well as the potential to sensitize the user to further exposure to thimerosal. Thimerosal was removed from the chlorhexidine solutions out of concerns over mercurial toxicity. However, the resulting solution continued to produce significant clinical problems due to the high concentration of chlorhexidine. Thimerosal continues to be replaced by mercury-free disinfecting agents out of concerns over mercurial toxicity.

Blanco shows the use of certain non-ionic surfactants to detoxify miramine in a contact lens solution containing thimerosal, Miramine and the surfactant. High ratios of surfactant to antimicrobial agent exceeding 11:1 appear to be preferred in Blanco, when ratios are calculated according to conventions herein. (Blanco expresses the antibacterial agent tris (2-hydroxyethyl)-tallow ammonium chloride concentrations as concentrations of "Miramine TA-30". Miramine TA-30 is nominally a raw material solution containing between 29.0 and 32.0 w/w % solids and from 10.0 to 17.0 w/w% of the active antimicrobial agent tris (2-hydroxyethyl)-tallow ammonium chloride.) However, Blanco does not show the use of polyethylene glycol ether-based non-ionic surfactants such as PEG 24 in ratios which enhance the antimicrobial activity of the antimicrobial agent.

Other, newer antibacterial agents are found to be more compatible with soft contact lenses. One such agent is a polymeric quaternary ammonium chloride compound known as Polyquad® (registered trademark of Alcon Laboratories, Inc.). Ophthalmic compositions containing Polyquad® and methods for disinfecting contact lenses with solutions containing this polymer are disclosed in U.S. Patent Nos. 4,526,346 and 4,407,791, both to Stark.

Another newer antibacterial agent for soft contact lens disinfection is a polyaminopropyl biguanide known as Cosmocil CQ® (registered trademark of ICI Americas, Inc.).

Although these antibacterial agents are effective as disinfectants to a substantial degree, there are still problems. Users may be at some risk for encountering lens contamination and developing ocular infections from fungi which are resistant to these antibacterial agents.

Accordingly, there is a need for improved ophthalmic compositions that can be used as disinfectants or preservatives for contact lenses without inflicting ocular irritation while retaining sufficient antibacterial and antifungal activities.

Summary of the Invention

It has been unexpectedly discovered that the presence of a non-ionic surfactant in a certain ratio to a quaternary ammonium antimicrobial agent leads to increased antimicrobial action far exceeding that previously noted for the same quaternary ammonium agent.

In one aspect, this invention relates to a thimerosal free ophthalmic composition for disinfecting contact lenses which comprises, in an aqueous and ocularly compatible system, an antibacterially and antifungally effective amount of a quaternary ammonium agent and an effective amount of a non-ionic surfactant, wherein the weight ratio of the non-ionic surfactant and the quaternary ammonium agent is from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1 and more preferably from about 1:1 to about 2:1.

Additionally, this invention encompasses a method of enhancing the antibacterial and antifungal activity of a quaternary ammonium agent in an aqueous, hypotonic, non-toxic, ophthalmic solution, the method

comprising combining with the quaternary ammonium agent an antibacterial and antifungal activity enhancing amount of a non-ionic surfactant.

In another aspect, this invention relates to a method for disinfecting contact lenses which comprises contacting the contact lenses with the above-described composition. Furthermore, this invention provides for a preserved disinfecting solution for contact lenses which comprises the above-described composition. In effect the present invention provides for a multipurpose rubbing, rinsing, disinfecting and storage ophthalmic solution for antibacterial and antifungal purposes, as well as for preserving and comfort drop usage.

Specific Embodiments

The quaternary ammonium antimicrobial agent for use in this invention must be effective in eliminating microorganisms from contact lenses and contact lens care products, and must be safe for use in disinfecting contact lenses as well as in preserving contact lens care products. Specific examples of quaternary ammonium antimicrobial agents include: cetylpyridinium chloride and tris (2-hydroxyethyl)-tallow ammonium chloride disclosed in U.S. Patent No. 4,029,817 to Blanco, or mixtures thereof. Monomeric and polymeric biguanides, such as chlorhexidine and the hexamethylene biguanides disclosed in U.S. Patent No. 4,758,595 to Bausch & Lomb, Inc. may also be considered. A preferred quaternary ammonium antimicrobial agent is tris (2-hydroxyethyl)-tallow ammonium chloride having the following formula:

$$\left[R - \begin{array}{c} CH_2 - CH_2 - OH \\ | \\ N^+ - CH_2 - CH_2 - OH \\ | \\ CH_2 - CH_2 - OH \end{array} \right] Cl^-$$

wherein R represents saturated or unsaturated alkyl residues derived from the hydrolysis of fatty acids and mixtures of those fatty acids predominantly containing 12 to 18 carbon atoms. The fatty acid source is preferably tallow. This compound is known as Miramine and has been sold as Miramine TA-30.

An antibacterially and antifungally effective amount of the foregoing active quaternary ammonium agent is that which effectively kills microorganisms or inhibits the growth thereof within a reasonable time. The U.S. FDA regulates contact lens disinfecting solutions and requires that standards of disinfection are met for a panel of microorganisms which are representative of the types of microorganisms found to be associated with contact lens contamination and ocular infections resulting therefrom. This panel, referred to as "the FDA Soft Lens Panel," consists of Pseudomonas aeruginosa, Candida albicans, Serratia marcescens, Staphylococcus epidermidis, and Asperaillus fumigatus. The FDA Soft Lens Panel also includes one virus, Herpes Simplex.

The disinfecting compositions of this invention are effective even at low concentrations against a wide spectrum of microorganisms, including but not limited to the above panel microorganisms. The amount of the quaternary ammonium agent to be used in this invention ranges from about 0.0002 w/v% to about 0.002 w/v%, preferably from about 0.0004 w/v% to about 0.0018 w/v%. When contemplating the use of the quaternary ammonium compound as a preservative in an ophthalmic saline solution or in a rewetting solution, the preferred range will be from about .0001 w/v% to about .0010 w/v%.

This invention employs an effective amount of a non-ionic surfactant to enhance the antibacterial and antifungal activity of the quaternary ammonium agent. Suitable non-ionic surfactants which can be used in this invention include, but are not limited to: polyethylene glycol fatty alcohol ethers such as PEG 24® described more fully below and polyoxyethylene

sorbitan fatty acid esters such as polyoxyethylene sorbitan monooleate (Polysorbate 80®, trademark of Atlas Chemical Company). Particularly preferred is PEG 24®, also known as ethoxyol 24, commercially available as Lipolan 31 from Lipo Chemicals, Inc.

It was unexpectedly found that within certain proportions the non-ionic surfactant, in combination with the quaternary ammonium agent, has a synergistic effect and gives a greater increase in the antibacterial activity and, more importantly, in the antifungal activity of the quaternary ammonium agent than previously noted for the same agent when used alone or outside the specific proportions, most notably in the absence of thimerosal. This finding is totally surprising, since enhancement of the antimicrobial activity of a quaternary ammonium compound has neither been noted by Blanco nor by any known prior art literature.

The amount of the non-ionic surfactant sufficient to enhance the antibacterial and antifungal activity of the quaternary ammonium agent will depend on a particular combination of the surfactant and the quaternary ammonium compound. Enhancement is seen with the weight ratio of the non-ionic surfactant to the quaternary ammonium agent being from about 1:1 to 10:1. Preferably, the weight ratios are in the range of from about 1:1 to about 5:1 and optimally from about 1:1 to about 2:1. The effective w/v percent of the non-ionic surfactant based on the total composition should, therefore, be in the range of from about 0.0002 w/v% to about 0.02 w/v%.

The ophthalmic composition of this invention may further comprise a plurality of ophthalmically acceptable vehicles well known to those skilled in the art of ophthalmic preparations, e.g., tonicity adjusting agents, buffering agents, chelating and stabilizing agents, viscosity modifiers and complexing agents. These vehicles must be non-toxic and must not distort the contact lens.

The tonicity adjusting agent is employed to adjust the osmotic value appropriate to microbiology, toxicology and lens compatibility considerations. Suitable tonicity adjusting agents include sodium and potassium chloride, propylene glycol, dextrose, calcium and magnesium chloride. The tonicity adjusting agents are present in the compositions in amounts of from about 0.01 w/v% to about 2.5 w/v%, preferably from about 0.1 w/v% to about 1.0 w/v%. The osmolality of the composition should be preferably adjusted to between about 200 to 280 mOsm/kg.

Suitable buffering agents include: sodium or potassium acetates, borates, phosphates, citrates; citric acid, boric acid, acetic acid; and various mixed phosphate buffers including combinations of Na_2HPO_4 and NaH_2PO_4. Generally, buffering agents may be present in amounts from about 0.01 w/v% to about 2.5 w/v%. The pH of the ophthalmic composition of this invention is adjusted to about 6.5 to about 7.8, preferably about 7.2 to 7.4.

Suitable chelating agents include ethylenediaminetetraacetic acid (EDTA) and its disodium salt, which are normally employed in amounts from about .005 w/v% to about 0.20 w/v%.

The viscosity modifier is used to adjust the viscosity of the composition to a desired level. Suitable viscosity modifiers include hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, polyvinyl alcohol, polyacrylamide, polyvinyl pyrolidone and others known to those skilled in the art. A preferred viscosity for the ophthalmic composition of this invention is from 3 to 200 cps (Brookfield Spindle).

Carboxymethyl cellulose, PVP and similar polymers known to those skilled in the art can additionally be used to further minimize any undesirable interaction (such as direct polymer surface adsorption or absorption of the quaternary ammonium agent onto the lens polymer during the lense care regimen soaking) between the quaternary ammonium agent and soft

hydrophilic contact lenses by complexing with the quaternary ammonium agent in solution.

A particularly preferred composition of the invention comprises: from about 0.0002 w/v% to about 0.002 w/v% [optimally from 0.0006 w/v% to 0.0018 w/v%] of tris (2-hydroxyethyl) ammonium chloride; from 0.0002 w/v% to about 0.02 w/v% [optimally from 0.0006 w/v% to 0.0090 w/v%] of PEG 24 as described more fully below; from about O w/v% to about 0.6 w/v% [optimally from 0.1 w/v% to 0.4 w/v%] sodium chloride; from about O w/v% to about 0.8 w/v% [optimally from O w/v% to 0.5 w/v%] propylene glycol; from about 0.5 w/v% to about 1.5 w/v% [optimally from 0.75 w/v% to 1.5 w/v%] of buffering agents; from about 0.005 w/v% to about 0.20 w/v% [optimally from 0.008 w/v% to .10 w/v%] of EDTA; from about O w/v% to about 0.10 w/v% [optimally from .01 w/v% to .08 w/v%] of carboxymethyl cellulose and sufficient water to total 100%, the composition having a pH value of from about 6.5 to about 7.8 [optimally from 7.2 to 7.4] and an osmolality of from about 200 mOsm/kg to about 280 mOsm/kg [optimally from 220 mOsm/kg to 260 mOsm/kg].

The ophthalmic compositions of this invention are ocularly non-toxic and compatible with all types of contact lenses. The compositions effect disinfection of contact lenses by chemical disinfection at ambient temperatures. The solutions may additionally be heated up to 100°C to promote faster disinfection if desired.

Typically, the contact lenses are rubbed with the solution or a suitable surfactant cleaner followed by a rinse with the solution and then placed in a suitable container with a sufficient amount of the composition to cover the lenses. The lenses are allowed to soak for preferably at least about 30 minutes and more preferably 2 to 8 hours to achieve the desired kill of bacteria, fungi and yeasts. Soaking for 2 to 8 hours has been shown to effectively disinfect the lenses. The soaking can be carried out at ambient

temperature or elevated temperatures. Following soaking, lenses may be rinsed with fresh solution prior to insertion.

This invention not only provides novel ophthalmic contact lens disinfecting compositions, but also provides novel preserved ophthalmic solutions such as contact lens rewetters, comfort drop solutions, and preserved saline solutions. The disinfecting compositions of this invention have significant advantages in terms of ocular toxicity and antimicrobial activity over the presently-used disinfectants or preservatives. Therefore, this invention provides for a simple, safe and effective disinfection system for all types of soft and hard contact lenses. The compositions and methods described herein also represent a definite improvement over those disclosed in Blanco. Blanco utilizes high concentrations of non-ionic surfactants and quaternary ammonium agents in preferred high ratios and depends upon the additional action of thimerosal to achieve its antifungal activity. The compositions of the present invention utilize low concentrations of non-ionic surfactants and quaternary ammonium agents in preferred low ratios to achieve antibacterial and antifungal activity without thimerosal. The non-ionic surfactants utilized in Blanco at high ratios are employed as detoxifying compounds; whereas, in the compositions of the present invention, the non-ionic surfactants are utilized at low ratios of surfactant to antimicrobial agent to enhance the activity of the antimicrobial agent. Additionally, solutions of lower Miramine content insure greater clinical safety and acceptance, especially if they are used secondarily as final lens rinse solutions that will unavoidably contact the ocular surface. The compositions of this invention can be used in this manner, whereas, the Blanco compositions are not designed as simple multi-purpose solutions.

The invention will be described in further detail below by way of the examples; however, it should be understood that these examples are for illustrative purposes only and do not purport to be wholly definitive as to conditions and scope of this invention. In the following experiments, all

concentrations are expressed as weight by volume (w/v) percent unless otherwise indicated.

EXAMPLE 1

A contact lens disinfecting composition was prepared by combining the following ingredients together in the manner indicated below:

	Percent
Miramine	0.0014
PEG 24*	0.0028
Propylene Glycol	0.4
NaCl	0.1
Citric Acid	0.219
Boric Acid	0.5
Sodium Borate	0.2
Na_2HPO_4 (heptahydrate)	0.2
NaH_2PO_4 (monohydrate)	0.09
EDTA	0.01
HCl or NaOH to adjust pH	
Distilled Water	q.s.

The ratio of PEG 24 to Miramine is 2:1. The above composition has a pH adjusted to 7.2 to 7.4 and an osmolality of about 240 mOsm/kg.

*PEG 24 is the 24 mole polyethylene glycol ether of the lanolin alcohol complex formed by the controlled hydrogenation of lanolin, and is sold under LIPOLAN 31® by Lipo Chemicals, Inc., and has the CAS Number 61790-81-6. In general PEG 24 is a polyethylene glycol ether of the hydrogenation product of a fatty acid.

The composition is preferably prepared by mixing two solutions, adding Miramine and adjusting the pH as follows. One solution is prepared by adding a suitable amount of purified water (not less than 5% of the final volume of water) to a stainless steel mixing vessel, equipped with propeller mixing and heated to 60° - 65° C. The heat source is then removed. PEG 24 is added slowly with rapid mixing until dissolved. The solution is then cooled with mixing and covered pending addition to the second solution.

The second solution is prepared by adding a suitable amount of purified water (not less than 75% of the final volume of water) to a mixing tank calibrated for final QS. The following ingredients are added with mixing, in order, allowing each to dissolve completely before adding the next:

Sodium Chloride
Citric Acid
Boric Acid
Sodium Borate
Sodium Phosphate dibasic heptahydrate
Sodium Phosphate monobasic
Disodium Edetate
Propylene Glycol

Thereafter the two solutions are combined with mixing. Miramine TA-30 is then added (by assay) to the mixture while mixing thoroughly. The pH is adjusted if necessary to 7.2 to 7.4 with sodium hydroxide (5N) or hydrochloric acid (5N). Any foam is allowed to dissipate and the solution is brought to final volume with the addition of purified water. The mixture is mixed thoroughly for at least 15 minutes, allowed to sit for at least about 12 hours, and the pH adjusted as necessary.

The solution is then sterile filtered through a 0.22 micron polysulfone or cellulose acetate filter by means of a pump or gravity into previously sterilized high density polyethylene plastic containers.

The antimicrobial activity of the above composition was tested against the panel of microorganisms required by the U.S. FDA guidelines for testing contact lens solutions for disinfective efficacy along with several additional microorganisms. Standard culture methods, harvest and quantitative microbiological analysis techniques were used. The organisms used for this purpose were: S. aureus, ATCC 6538; P. aeruginosa, ATCC 15442; E. Coli, ATCC 8739; C. albicans, ATCC 10231; A. niger, ATCC 16404; S. marcescens, ATCC 14041; S. epidermitis, ATCC 17917; and A. fumigatus, ATCC 10894.

A D-value was determined after 6 hours' contact with the microorganisms using the standard method for D-value determination. See Pflug IJ, Holcomb RG, "Principles of Thermal Destruction of Microorganisms" in: Block SS, ed. Disinfection, Sterilization, and Preservation, 3rd ed., Philadelphia, Lea & Febiger, 1983:751-810; Houlsby RD, "An Alternate Approach for Preservative Testing of Ophthalmic Multiple-dose Products", J. Parenter Drug Assoc. 1980; 34(4):272-6; and Bruch MK, "The Regulation of Hydrophilic Contact Lenses by the Food and Drug Administration", Dev. Ind. Microbiol., 1976; 17:29-47.

The test results as expressed in terms of D values are illustrated in Table 1.

TABLE 1

	ORGANISMS							
	Sa	Pa	Ec	Ca	An	Sm	Se	Af
D-values Time (minutes)	<80	<80	108	95	600	113	82	109

The above results show that the 0.0014% Miramine in combination with 0.0028% PEG 24 has a good antimicrobial spectrum, including antifungal activity.

EXAMPLE 2

A contact lens disinfecting composition was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.0002
PEG 24	0.0002
Propylene Glycol	0.4
NaCl	0.1
Citric Acid	0.219
Boric Acid	0.5
Sodium Borate	0.2
Na_2HPO_4 (heptahydrate)	0.2
NaH_2PO_4 (monohydrate)	0.09
EDTA	0.01
HCl or NaOH to adjust pH	
Distilled Water	q.s.

The ratio of PEG 24 to Miramine is 1:1. The above composition has a pH of 7.3 and an osmolality of about 240 mOsm/kg.

The composition shows adequate antimicrobial activity against P. aeruginosa and C. albicans, with D-values of 157 and 240 minutes, respectively.

EXAMPLE 3

A contact lens disinfecting composition was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.0004
PEG 24	0.0004
Propylene Glycol	0.4
NaCl	0.1
Citric Acid	0.219
Boric Acid	0.5
Sodium Borate	0.2
Na_2HPO_4 (heptahydrate)	0.2
NaH_2PO_4 (monohydrate)	0.09
EDTA	0.01
HCl or NaOH to adjust pH	
Distilled Water	q.s.

The ratio of PEG 24 to Miramine is 1:1. The above composition has a pH of 7.3 and an osmolality of about 240 mOsm/kg.

The composition shows good antimicrobial activity against S. marcescens, P. aeruginosa, C. albicans, and A. fumigatus, with D-values of 189, 106, 133 and 200 minutes, respectively.

EXAMPLE 4

A contact lens disinfecting composition was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.0010
PEG 24	0.0010
Propylene Glycol	0.4
NaCl	0.1
Citric Acid	0.219
Boric Acid	0.5
Sodium Borate	0.2
Na_2HPO_4 (heptahydrate)	0.2
NaH_2PO_4 (monohydrate)	0.09
EDTA	0.01
HCl or NaOH to adjust pH	
Distilled Water	q.s.

The ratio of PEG 24 to Miramine is 1:1. The above composition has a pH of 7.3 and an osmolality of about 240 mOsm/kg.

The composition shows excellent antimicrobial activity against S. marcescens, P. aeruginosa, C. albicans, and A. fumigatus with 6 hour D-values of 138, 90, 133 and 144 minutes, respectively.

EXAMPLE 5

A contact lens disinfecting composition was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.002
PEG 24	0.002
Propylene Glycol	0.4
NaCl	0.1
Citric Acid	0.219
Boric Acid	0.5
Sodium Borate	0.2
Na_2HPO_4 (heptahydrate)	0.2
NaH_2PO_4 (monohydrate)	0.09
EDTA	0.01
HCl or NaOH to adjust pH	
Distilled Water	q.s.

The ratio of PEG 24 to Miramine is 1:1. The above composition has a pH of 7.3 and an osmolality of about 240 mOsm/kg.

The composition shows good antimicrobial activity against S. marcescens, P. aeruginosa, C. albicans, and A. fumigatus, with 6 hour D-values of 124, 72, 90 and 103 minutes, respectively.

EXAMPLE 6

A contact lens disinfecting composition containing carboxymethyl cellulose was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.0014
PEG 24	0.0028
Propylene Glycol	0.4
NaCl	0.1
Citric Acid	0.219
Boric Acid	0.5
Sodium Borate	0.2
Na_2HPO_4 (heptahydrate)	0.2
NaH_2PO_4 (monohydrate)	0.09
EDTA	0.01
Carboxymethylcellulose	0.02
HCl or NaOH to adjust pH	
Distilled Water	q.s.

The ratio of PEG 24/Miramine is 2:1. The above composition has a pH of 7.3 and an osmolality of about 240 mOsm/kg. The composition shows good antimicrobial activity against S. marcescens, C. albicans, A. fumigatus and A. niger, with 6 hour D-values of 225, 64, 240 and 277 minutes, respectively. This composition further minimizes the interaction of Miramine with contact lenses, showing 49% of the Miramine-lens interaction of the composition in EXAMPLE 1. This result is due to the addition of carboxymethyl cellulose to the composition.

EXAMPLE 7

A contact lens disinfecting composition was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.0007
PEG 24	0.0014
NaCl	0.25
Boric Acid	0.9
Sodium Borate	0.2
Edetate disodium	0.01
Sodium Carboxymethylcellulose	0.02
HCl or NaOH to adjust pH	
Distilled Water	q.s

The ratio of PEG 24/Miramine is 2:1. The above composition has a pH of 7.3 and an osmolality of about 245 mOsm/kg. This composition further minimizes the accumulation of Miramine on contact lenses compared to the composition in EXAMPLE 6. This result is due to the lower concentration of Miramine.

EXAMPLE 8

An ophthalmic preserved saline composition was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.0004
PEG 24	0.0008
NaCl	0.5
Boric Acid	0.39
Sodium Borate	0.2
Distilled Water	q.s.

The ratio of PEG 24/Miramine is 2:1. The above composition has a pH adjusted to 7.4 and an osmolality of about 230 mOsm/kg.

EXAMPLE 9

An ophthalmic preserved artificial tear composition was prepared by combining the following ingredients together essentially according to the procedure of EXAMPLE 1.

	Percent
Miramine	0.0004
PEG 24	0.0040
NaCl	0.5
Sodium Lactate	0.03
KCl	0.31
Sodium Carboxymethylcellulose	1.00
HCl or NaOH to adjust pH	
Distilled Water	q.s

The ratio of PEG 24/Miramine is 10:1. The above composition has a pH of 6.5 and an osmolality of about 265 mOsm/kg.

EXAMPLE 10

An experiment was conducted to demonstrate the differential antimicrobial efficacy of various contact lens disinfecting compositions with and without thimerosal.

Composition No.	Description
1	Composition of EXAMPLE 1 14 ppm Miramine; 2:1 PEG 24:Miramine Ratio
2	Composition with 138 ppm Miramine, 23 ppm Thimerosal, 14.5:1 Polysorbate 80:Miramine Ratio
3	Composition of No. 2 above without Thimerosal
4	Composition with 138 ppm Miramine, 23 ppm Thimerosal 14.5:1 PEG 24: Miramine Ratio
5	Composition of No. 4 above without Thimerosal

A D-value was determined after 4 hour contact with the indicated microorganisms using the method detailed in EXAMPLE 1.

The test results as expressed in terms of D-values (in minutes) are illustrated in Table 2 below.

TABLE 2

	Organisms D-values (minutes)							
Composition	Sa	Pa	Ec	Ca	An	Sm	Se	Af
1	42	80	41	218	300	80	21	120
2	21	60	41	43	65	62	41	126
3	42	NK*	218	300	NK	NK	63	NK
4	42	60	41	73	42	100	68	120
5	42	NK	300	240	NK	NK	21	NK

*NK = No Kill

The results of Table 2 illustrate that with the exception of composition No. 1 above, in the absence of Thimerosal, the Miramine solutions with high surfactant to quaternary ammonium agent ratio have reduced antibacterial and antiyeast activity and no antifungal activity.

EXAMPLE 11

Several experiments were performed to determine the antimicrobial activity of miramine in the absence of PEG 24 and in the presence of varying concentrations of PEG 24.

A composition of 0.001 miramine without any amount of PEG 24 was used as control. The control composition was prepared by following the procedure of EXAMPLE 1 and had all the ingredients that were disclosed therein, except PEG 24, at their respectively indicated concentrations.

Compositions of 0.001%, 0.005%, 0.010%, and 0.015% PEG 24 were prepared similarly by having incorporated all the ingredients including 0.001% Miramine. Compositions were tested against S. marcescens (ATCC 14041), P. aeruginosa (ATCC 15442), C. albicans (ATCC 10231) and A. fumigatus (ATCC 10894). After 6 hours' contact time, D-values were determined. The results are shown below in Table 3. Replicates were additionally run for S. marcescens, P. aeruginosa and C. albicans for 1:1, 5:1 and 10:1 ratio solutions.

TABLE 3

PEG 24 Concentration (%) (Ratio)	Organisms D-values (minutes) Sm	Pa	Ca	Af
0	>1500, -	100, -	>1500, -	not tested
0.001 (1:1)	168, 138	72, 90	116, 133	144
0.005 (5:1)	337, 257	90, 116	133, 138	129
0.010 (10:1)	978, 600	100, 72	187, 164	116
0.015 (15:1)	>1500, -	90, -	295, -	not tested

A lower D-value is indicative of more effective antimicrobial activity. The result of Table 3 illustrate that PEG 24 enhances the antimicrobial activity of Miramine at ratios of from 1:1 to 10:1. The 0.001% Miramine without PEG 24 shows little antimicrobial activity.

EXAMPLE 12

Table 4 shows comparative antimicrobial activity of 0.0014% miramine compositions. All compositions were tested against S. marcescens (ATCC 14041), S. epidermitis (ATCC 17917), P. aeruginosa (ATCC 15442), C. albicans (ATCC 10231), and A. fumigatus (ATCC 10894). After 6 hours contact time, D-values were quantified.

TABLE 4

PEG 24 Concentration (w/v%) (Ratio)	Organisms D-values (minutes) Sm	Se	Pa	Ca	Af
0	515	117	167	>3000	>1500
0.0014 (1:1)	109	72	90	120	180
0.007 (5:1)	212	72	72	124	180
0.014 (10:1)	515	<62	<60	225	538
0.021 (15:1)	688	<62	118	320	538

The results of Table 4 again illustrate that PEG 24 enhances the antimicrobial activity of Miramine at ratios of from 1:1 to 10:1. The 0.0014% Miramine solution without PEG 24 shows some antibacterial activity but no significant antifungal activity (A. fumigatus activity) or activity against yeast (C. albicans activity). Thus, potentiation of the antifungal activity and activity against yeast of Miramine by PEG 24 is particularly apparent.

EXAMPLE 13

Several experiments were performed to determine the antimicrobial activity of Miramine in the presence of varying concentrations of Polysorbate 80.

Compositions were prepared by following the procedure of EXAMPLE 1 and had all the ingredients that are disclosed therein, except PEG 24 which was replaced by Tween 80. All ingredients were added at their respectively indicated concentrations in EXAMPLE 1.

Compositions containing 0.0014%, 0.0028%, 0.0070%, 0.0140% and 0.0210% Tween 80 were prepared. All solutions were adjusted to pH 7.3. Osmolality for all solutions was 240 mOsm/kg.

Compositions were tested against S. marcescens (ATCC 14041), S. aureus (ATCC 6538), S. epidermitis (ATCC 17917), P. aeruginosa (ATCC 15442), C. albicans (ATCC 10231), and A. fumigatus (ATCC 10894). Six hour D-values are shown below in Table 5.

TABLE 5

Polysorbate 80 Concentration (%) (Ratio)	Organisms D-values (minutes) Sm	Sa	Se	Pa	Ca	Af
0*	515	-	117	167	>3000	>1500
0.0014 (1:1)	114	90	72	90	61	130
0.0028 (2:1)	102	72	61	90	92	130
0.0070 (5:1)	141	72	61	90	61	130
0.0140 (10:1)	425	72	72	90	90	202
0.0210 (15:1)	662	62	61	185	180	462

* Same control solution as in Example 11.

The results of Table 5 illustrate that Tween 80, like PEG 24, enhances the antimicrobial activity of Miramine, with an optimum ratio of 2:1.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made without departing from the spirit or scope of the invention.

What is claimed is:

1. A thimerosal free ophthalmic composition for disinfecting contact lenses which comprises, in an aqueous, ocularly compatible system, an antibacterially and antifungally effective amount of a quaternary ammonium agent and an effective amount of a non-ionic surfactant, wherein the weight ratio of the non-ionic surfactant to the quaternary ammonium agent is from about 1:1 to 10:1.

2. The ophthalmic composition of claim 1, wherein the quaternary agent is selected from the group consisting of cetylpyridinium chloride and tris (2-hydroxyethyl)-tallow ammonium chloride or mixtures thereof.

3. The ophthalmic composition of claim 2, wherein the quaternary ammonium agent is tris (2-hydroxyethyl)-tallow ammonium chloride.

4. The ophthalmic composition of claim 1, wherein the weight ratio of the non-ionic surfactant to the quaternary ammonium agent is from about 1:1 to about 5:1.

5. The ophthalmic composition of claim 1, wherein the quaternary ammonium agent is present in an amount from about 0.0002 w/v% to about 0.002 w/v%.

6. The ophthalmic composition of claim 5, wherein the quaternary ammonium agent is present in an amount from about 0.0006 w/v% to about 0.0018 w/v%.

7. The ophthalmic composition of claim 1, wherein the weight ratio of the non-ionic surfactant to the quaternary ammonium agent is from about 1:1 to about 2:1.

8. The ophthalmic composition of claim 1, wherein the non-ionic surfactant is selected from the group consisting of polyethylene glycol fatty alcohol ethers and polyoxypropylene sorbitan fatty acid esters.

9. The ophthalmic composition of claim 8, wherein the non-ionic surfactant is PEG 24.

10. The ophthalmic composition of claim 9, wherein the quaternary ammonium compound is tris (2-hydroxyethyl)-tallow ammonium chloride.

11. The ophthalmic composition of claim 1, which further comprises an ophthalmically acceptable vehicle.

12. The ophthalmic composition of claim 11, wherein the ophthalmically acceptable vehicle is one or more members selected from the group consisting of a tonicity adjusting agent, buffering agent, chelating and stabilizing agents, a viscosity modifier and a complexing agent.

13. An ophthalmic composition which comprises, in an aqueous, ocularly compatible system: from about 0.0002 w/v% to about 0.002 w/v% of tris (2-hydroxyethyl)-tallow ammonium chloride; from 0.0002 w/v% to about 0.02 w/v% of PEG 24, from about O w/v% to about 0.6 w/v% of sodium chloride; from about O to about 0.8 w/v% propylene glycol; from about 0.5 w/v% to about 1.5 w/v% of buffering agents; from about 0.005 w/v% to about 0.20 w/v% of EDTA; from about O w/v% to about 0.10 w/v% of carboxymethyl cellulose; and sufficient water to total 100%, the composition having a pH of from about 6.5 to about 7.8 and an osmolality of from about 200 mOsm/kg to about 280 mOsm/kg.

14. The ophthalmic composition of claim 13, which further comprises from about 0.01 w/v% to from about 10 w/v% of a viscosity modifier.

15. The ophthalmic composition of claim 13, wherein the weight ratio of the non-ionic surfactant to the quaternary ammonium agent is from about 1:1 to about 5:1.

16. A method of disinfecting contact lenses comprising contacting a contact lens with an effective amount of an ophthalmic composition for a period sufficient to disinfect the lens, the ophthalmic composition comprising, in an aqueous, Thimerosal free, ocularly compatible system an antibacterially and antifungally effective amount of a quaternary ammonium agent and an effective amount of a non-ionic surfactant to enhance the antibacterial and antifungal activity of the quaternary ammonium agent, wherein the weight ratio of the non-ionic surfactant to the quaternary ammonium agent is from about 1:1 to 10:1.

17. The method of claim 16, wherein the contact lens is a soft contact lens.

18. The method of claim 16, wherein the quaternary ammonium compound is tris (2-hydroxyethyl)-tallow ammonium chloride and the non-ionic surfactant is a polyethylene glycol ether of the hydrogenation product of a fatty acid.

19. The method of claim 18, wherein the tris (2-hydroxyethyl)-tallow ammonium chloride is present in an amount of from 0.0002 w/v% to about 0.002 w/v%.

20. A method of enhancing the antibacterial and antifunqal activity of a quaternary ammonium agent in an aqueous, Thimerosal free,

non-toxic, hypotonic ophthalmic solution, the method comprising combining with the quaternary ammonium agent, an antibacterial and antifungal activity enhancing amount of a non-ionic surfactant.

21. The method of claim 20, wherein the non-ionic surfactant and the quaternary ammonium agent are combined at the ratios of from about 1:1 to 10:1.

22. The method of claim 20, wherein the quaternary ammonium compound is tris (2-hydroxyethyl)-tallow ammonium chloride and the non-ionic surfactant is PEG 24.

23. The method of claim 21, wherein the antibacterial activity of tris (2-hydroxyethyl)-tallow ammonium chloride has been enhanced against Serratia marcescens, Staphylococcus epidermitis, and Pseudomonas aeruginosa.

24. The method of claim 21, wherein the antiyeast and antifungal activity of tris (2-hydroxyethyl)-tallow ammonium chloride has been enhanced against Candida albicans and Aspergillus fumigatus.

25. A multi-purpose ophthalmic Thimerosal free composition comprising an antibacterially and antifungally amount of a disinfecting agent and an amount of a non-ionic surfactant to enhance the antibacterial and antifungal activity of the disinfecting agent.

26. The composition of claim 25 wherein the disinfecting agent is a quaternary ammonium compound.

27. The composition of claim 25 wherein the disinfecting agent is tris (2-hydroxyethyl)-tallow ammonium chloride.

28. The composition of claim 25 wherein the ratio of the surfactant to the disinfecting agent is from about 1:1 to 10:1.

29. The composition of claim 28 wherein the ratio is from about 1:1 to about 5:1.

30. The composition of claim 28 wherein the ratio is from about 1:1 to about 2:1.

31. The ophthalmic composition of claim 1 wherein the weight ratio is 1:1.

32. The ophthalmic composition of claim 1 wherein the weight ratio is 2:1.

33. The ophthalmic composition of claim 1, wherein the quaternary ammonium agent is cetylpyridinium chloride.

34. The ophthalmic composition of claim 13, wherein the weight ratio of the non-ionic surfactant to the quarternary ammonium agent is from about 1:1 to about 5:1.

35. The method of claim 16 wherein the weight ratio is from about 1:1 to about 5:1.

36. The method of claim 16 wherein the weight ratio is from about 1:1 to about 2:1.

37. The method of claim 20 wherein the weight ratio is from about 1:1 to about 5:1.

38. The method of claim 20 wherein the weight ratio is from about 1:1 to about 2:1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/02176

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61L2/18; G02C13/00; C11D1/835

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61L ; C11D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US,A,4 029 817 (M.BLANCO) 14 June 1977 cited in the application see column 4, line 33 - line 57; claims; examples	1-4,8, 11-19
A	GB,A,1 292 412 (BARNES HIND PHARMACEUTICALS) 11 October 1972 see page 1, line 15 - line 31	1-2,20
A	US,A,4 336 151 (B. LIKE) 22 June 1982 see column 3, line 25 - line 37	

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21 AUGUST 1992	04. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.COUSINS-VAN STEEN

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ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9202176 SA 59260

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 21/08/92
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		JP-B- 54010615	08-05-79
		NL-A- 7410457	26-03-75
GB-A-1292412	11-10-72	None	
US-A-4336151	22-06-82	None	

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